Remarks

Claims 38-43 and 46 are pending. The Examiner is thanked for the courtesy of a telephone interview on May 17, 2006.

The claimed invention

There is one independent claim and five dependent claims currently pending. The independent claims require a selenocysteine-containing peptide to be fused to a surface protein displayed on the surface of an amplifiable genetic particle.

The specification describes how selenocysteine is incorporated into the peptide and how through genetic fusion to a surface protein, the peptide is displayed on the surface of the amplifiable particle. The requirement for introducing a selenocysteine into a peptide that is fused to a surface protein and therefore is made during the replication of the amplifiable genetic particle is novel. Previously, peptides displayed on the surface of the amplifiable particle contained amino acids from the standard 20 amino acid repertoire only. An advantage of introducing a selenocysteine into the displayed peptide is that the selenocysteine can be modified and a functional group can be attached to the peptide through this 21st amino acid. The novel steps for introducing a selenocysteine into a peptide fused to a surface protein displayed on the surface of an amplifiable genetic particle are summarized in the figures discussed with the Examiner and also below.

Figure 1 shows a UGA, which is a stop codon that is recoded for selenocysteine by the presence of a specific downstream stem loop structure (SECIS). During the course of translation, a specific tRNA, which carries the selenocysteine species, can participate in translation in response to the UGA codon if and only if there is a downstream element. This is mediated by an elongation factor. A detailed explanation of the manner in which selenocysteine is incorporated into a protein is provided in the specification on pages 5-11.

Figure 2 shows a naturally occurring bacterial SECIS with a long stem structure. Base pairing of the lowest 11 nucleotides in the hairpin was found to be unnecessary to selenocysteine insertion. One embodiment of the present invention was to substitute this sequence of nucleotides with a sequence of desired nucleotides or a random nucleotide sequence to generate a foreign context exemplified in Figure 4. In Figure 4, selenocysteine is introduced in the context of a random peptide library fused to M13 pIII (surface protein). However, any surface protein could be substituted for the M13 pIII.

Figure 5 demonstrates that selenocysteine incorporation and plaques are dependent on selenocysteine being present in the media.

Figure 7 shows specific chemical modification of a displayed selenopeptide under conditions where the corresponding cysteine-containing pepetide is unreactive.

As can be seen clearly in Figure 4, the DNA encoding the peptide sequence containing the selenocysteine can be fused to another DNA

sequence encoding a protein or peptide including any surface protein sequence known in the literature from any amplifiable genetic particle. One of ordinary skill in the art would appreciate that no special chemistry is required to achieve a fusion between the selenocysteine containing peptide and any desired surface protein.

Rejections under 35 U.S.C.§102 and 35 U.S.C.§103

Applicants would like to first reiterate that they are unaware of (a) any attempt in the prior art to achieve the claimed fusion protein involving selenocysteine expression to express variants of proteins on the surface of genetic particles; or (b) any description of incorporation of selenocysteine into a foreign context using existing biosynthetic machinery.

Nonetheless, in the final office action mailed 12/21/05, the Examiner maintained a novelty and obviousness rejection based on Larson and Hollinger either alone or combination which has no merit. There is no suggestion in either reference that they be combined and even if they were combined they would not teach the present invention.

The Larson reference

The Larson reference describes the intracellular expression of enzymes that naturally contain selenocysteine. There is no suggestion that this protein be expressed within a genetically amplifiable particle nor that the selenocysteine containing peptide be fused to a surface protein.

The Examiner has disregarded the applicants' comments and misinterpreted the reference for a second time. The Examiner's comments are factually incorrect.

For example, the Examiner incorrectly states that Larson teaches the use of M13 phage to recombinantly express selenopeptides. In fact, the reference utilizes M13 phage as a vector in site directed mutagenesis and recombinant expression of the selenopeptide is described in eukaryotic or prokaryotic cells only. Moreover, there is no teaching or suggestion that a selenocysteine peptide be fused to a surface protein.

A global search for "phage" revealed only one mention of M13 in the entire lengthy patent. The reference states:

> " Typical vectors useful in site directed mutagenesis include vectors such as the M13 phage ..." (column 15, line 65). "This heteroduplex vector [resulting from site directed mutagenesis] is then used to transform appropriate cells..." (column 16, lines 22-24).

It should be noted that "cells" refers to eukaryotic or prokaryotic cells (column 17, line 58) in which the protein is either expressed intracellularly and the cells are lysed (column 17, line 16) or the protein is secreted (column 16, line 60). Moreover, as stated in the previous response dated August 17, 2005, the term "surface" could not be found in the text by a global computer search.

In summary, this reference does not suggest or teach making a selenocysteine containing peptide fused to a surface protein displayed on an amplifiable particle.

Applicants provided detailed comments in response to the first office action with respect to Larson on pages 15 and 16 of the office action response dated August 17, 2005.

The Holliger Reference

The Holliger reference describes secretion of an enzyme from a recombinant host. The Examiner states "Holliger teaches peptides fused to the N-terminus of the M13 coat protein." However, this reference teaches a study of how phage infect their bacteria and in particular the membrane penetration domains on g^3p and the structural properties of these domains. This reference describes the solution structure of the g^3p, a minor coat protein from filamentous phage fd. Although g^3p is used in phage display libraries there is nothing in this reference that discusses types of peptides fused to the g^3p and nothing that suggests that selenocysteine be incorporated into a peptide fused to g^3p.

Additional discussion of the Holliger reference can be found on pages 16 and 17 of the office action response dated August 17, 2005.

Applicants respectfully submit that the references do not describe the present claimed invention either inherently or explicitly and request that the Examiner reverse the rejection.

Applicants again assert that the Sandman references are not prior art. The applicants filed the provisional application and then submitted two papers corresponding to the provisional application. These papers by the applicants were published in 2000 about a year after the provisional application was filed.

Rejection under 35 U.S.C.§ 112

The Examiner has rejected the claims with respect to the peptide portion, the surface protein and the amplifiable particle. This rejection makes no sense to Applicants in light of the previous response explaining that these aspects are well known in the art and are not part of the novel aspects of the invention. Any person of ordinary skill would understand the meaning of these terms, which are used for example in references and patents relating to phage display (see for example US 5,233,409). Additional discussion of why these terms meet the description requirement is provided on pages 9 and 10 of the response dated August 17, 2005.

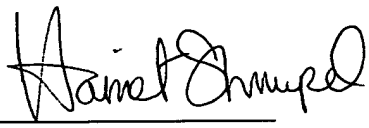
Summary

For the reasons set forth above, Applicants respectfully submit that this case is in condition for immediate allowance. Early and favorable consideration leading to prompt issuance of this Application is earnestly solicited.

Applicants petition for a 2-month extension of time to file a response and enclose a check in the amount of $475.00, which covers the extension fee and the fee for attached notice of appeal. Please charge Deposit Account No. 14-0740 for any deficiencies.

Respectfully submitted,

NEW ENGLAND BIOLABS, INC.



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